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16. ABSTRACT

A pressing need in the field of environmental neurotoxicology continues to be the development and validation of neurobehavioral test methods. It was appropriate therefore, that this conference focused on the applicability of different test methods to the assessment of nervous system dysfunction. The conference organizers are to be commended for bringing together such a diverse group of scientists whose research interests range from the molecular level to the level of complex behaviors and whose experiments vary from carefully controlled in vitro studies to studies on human populations inadvertently exposed to toxic substances. Many important concepts in neurotoxicology were raised in the presentations and I will attempt to highlight these in my summary remarks.

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Summary Remarks

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A pressing need in the field of environmental neurotoxicology continues to be the development and validation of neurobehavioral test methods. It was appropriate therefore, that this conference focused on the applicability of different test methods to the assessment of nervous system dysfunction. The conference organizers are to be commended for bringing together such a diverse group of scientists whose research interests range from the molecular level to the level of complex behaviors and whose experiments vary from carefully controlled in vitro studies to studies on human populations inadvertently exposed to toxic substances. Many important concepts in neurotoxicology were raised in the presentations and I will attempt to highlight these in my summary remarks.

Obviously, the ultimate goal of environmental neurotoxicology is to accurately predict the neurobehavioral consequences of toxicant exposure in human populations. In dealing with a chemical of unknown toxicity, tests must first be performed to determine whether the nervous system is a target organ for that chemical (i.e., screening). As our understanding increases, more specific questions are asked regarding its neurotoxicity. These include characterizing the nature of the effects, determining dose- and time-effect relationships, and understanding mechanisms of action. Clearly, different experimental approaches and methodologies will be required at each level of inquiry and it is important therefore that the methods which were discussed at this conference be viewed in that context.

The complexity of the nervous system and the potential for toxicants to act on a wide variety of target sites within the nervous system makes it unlikely that an "Ames Test" for neurotoxicity will ever be developed. Whereas the Ames test deals with changes in genetic material, which is regarded to be the target site of mutagenic and carcinogenic chemicals, the detection of neurotoxicity requires a thorough investigation of diverse levels of neural organization which are unlikely to be represented in a single in vitro system. Therefore, although the potential value of a single in vitro system to screen for neurotoxicity seems limited, the selection of an appropriate spectrum of tests may provide an accurate prediction of neurotoxicity. On the other hand, if the existing data on a chemical suggest that a particular type of neurotoxic effect is produced (e.g., impaired neurotransmission), then selection of an appropriate in vitro test system can provide important information on the mechanism of action of that chemical (e.g., see Rowan, this volume). This approach is also useful for the prioritization of chemicals within a chemical class since data can be collected on the relative toxicity of the individual chemicals.

A variety of in vitro test systems was discussed at this symposium including synaptosomal preparations, tissue cultures, invertebrate nerve preparations, and mammalian neuromuscular preparations. Each of these offers some advantages in evaluating certain aspects of neurotoxicity. Dr. Bierkamper, for example, reported how the observation that exposure to triethyltin results in muscular dysfunction stimulated experiments to determine the mechanism of action of triethyltin utilizing an isolated neuromuscular preparation. As he indicated, understanding the mechanism of action can lead to studies of structure-activity relationships, as well as a better understanding of therapy and prevention.

However, in vitro systems have several limitations in the study of environmental neurotoxicants. For example, their use is limited if the onset of toxicity is slow. In this case steps must be taken to utilize preparations which will remain viable for extended periods of time thus allowing adequate time to study the development of a neurotoxic response. Dr. Hooisma discussed how organotypic cultures of nervous tissue may hold promise in this area since they can be maintained for long periods of time and thus allow for the study of neurotoxic effects which have a delayed onset.

Another limitation of in vitro systems concerns the toxicokinetics of a chemical. Neurotoxicants which require metabolic activation cannot be adequately characterized if the in vitro test system does not contain the necessary enzymes to convert the parent compound to its active metabolite, and/or if the in vitro metabolic fate of the chemical is unknown. Furthermore, in vitro systems may have limited value is extrapolating risk to man since the conditions of in vivo exposure are not faithfully represented. Dr. Silbergeld, for example, suggested that accumulation of delta aminolevulinic acid, resulting from the inhibition of ALA dehydratase, may be indirectly contributing to the neurotoxicity of lead; in vitro systems would not have detected such an effect. As was pointed out by Dr. Habermann, studies with in vitro systems will require confirmation in the whole animal.

Papers presented in the two sessions on animal studies dealt with a variety of methodological approaches. When viewed in their entirety, they illustrate how the proper integration of behavioral, neurophysiological, neurochemical, and neuropathological test methods is essential to our understanding of neurotoxicity and how no single approach to neurobehavioral testing will provide all the needed information on the neurotoxicity of a chemical. Obviously different approaches have different inherent potentials for screening, characterizing, and determining mechanisms of action.

Behavioral methods seem best suited for detecting and characterizing the functional alterations brought about by exposure to toxicants. Dr. Lehotzky made the important point, which is sometimes forgotten, that the LD50 is insufficient in characterizing the toxicity associated with long-term exposure to a neurotoxicant; her work showed that using the appropriate behavioral tests, the neurotoxicity of pesticides was clearly evident at exposure levels below those associated with overt toxicity. Dr. Bornhausen provided similar data on animals exposed prenatally to toxic substances.

A number of papers was concerned with characterizing the neurotoxicity associated with exposure to various classes of chemicals including heavy metals, pesticides and solvents. The utility of schedule-controlled performance measurements to precisely define the nature of behavioral disruption produced by methyl mercury exposure in pigeons was demonstrated in Dr. Laties' presentation. The adaptability and partial recovery of the organism was also demonstrated and while there is clearly a danger in extrapolating from data on one animal, his findings illustrate how the use of stable baselines of performance can lead to a better understanding of the relationship between toxic chemicals and their effects on behavior. Dr. Fox's use of psychophysical techniques, in combination with pharmacological probes, to reveal visual deficits in animals developmentally exposed to lead, is another example of how precisely controlled behavioral and electrophysiological experiments are ideally suited for characterizing subtle neurotoxic effects.

In addition to characterizing the functional consequences of toxicant exposure, properly designed neurobehavioral experiments also provide insight as to mechanisms of neurotoxicity. Dr. Tilson, for example presented data on the behavioral effects of exposure to tetraethyl lead. Based on the results of these studies, a series of hypotheses was formulated regarding the nature of the toxic insult which in turn permitted pharmacological and neurochemical experiments to be performed of the mechanism of action. This paper clearly illustrates the power of a multidisciplinary approach to the study of neurotoxicity.

As new methods are applied to the study of neurotoxicity, there is a need to evaluate their utility and define their limitations. In this case, the method must be systematically validated using known neurotoxicants. This kind of systematic approach is essential if we are to have confidence in the ability of our test methods to detect a wide range of neurotoxic effects. In his presentation, Dr. Dyer showed that different electrophysiological measurements can be used as sensitive assays of dysfunction produced by trimethyltin. For example, the visual evoked potential detected visual system abnormalities which had not been suspected previously. Unfortunately, our understanding of these electrical events is still incomplete and therefore the implication of these observed alterations remains speculative.

A very practical issue was raised by the solvent-solvent interaction studies reported by Dr. Altenkirch. We live in an environment in which exposure to multiple chemicals is the rule rather than the exception. Developing research strategies to address these chemical interactions is one of the greatest challenges facing the environmental toxicologist.

Finally, a number of studies dealt with the mechanisms of action of a variety of neurotoxicants, most notably lead and N-hexane. The very elegant studies of Dr. Graham on the mechanism of hexane-induced neuropathy should be an inspiration to us all. Certainly it is from an understanding of mechanisms of action that the most reasonable extrapolations to humans will be made. With the myriad of chemicals present in the environment, it is impractical to study each as extensively as some of the compounds discussed here (e.g., lead), and we must therefore develop methods to generalize from one chemical to another. This is perhaps best done through an understanding of mechanisms.

Although neurotoxicity data derived from carefully controlled human studies provide the most directly relevant information for the development of risk assessment, the number of laboratory and field studies in this area has been quite limited. The number of papers presented in the two sessions devoted to human effects is encouraging and indicates that a number of laboratories, particularly in Europe, are beginning to engage in these kinds of studies.

A number of important issues was raised in these presentations. One important issue concerns the need to identify proper controls. In many instances, "matched controls" are used although one can never be certain that proper control is exercised over all relevant variables. In other cases, test parameters have been characterized with respect to how certain factors contribute to the overall variability; however, one is always concerned about how these factors influence the detection of a treatment effect.

Another issue concerns the precise determination of toxicant exposure levels. Since dose-response data are essential to any estimate of risk, some measure of exposure is needed. Yet in field studies, particularly those which evaluate environmental exposure, the question of exposure history is a chronic problem. The use of occupationally exposed workers, where careful health records are maintained, provides some estimate of exposure but even this type of data cannot substitute for measurements of body burden.

As the availability of field testing capability increases, the use of these data should be expanded to provide more direction to the experimental neurotoxicologist. By better coordinating laboratory and field studies, hypotheses can be formulated and tested in the laboratory. Information derived from "environmental incidents," for example, should provide insight as to the types of neurotoxic effects produced by exposure to any given chemical.

Development of appropriate methodology for human testing is a research area that requires considerable attention and presents a considerable challenge. Unlike measurements used in laboratory animals, techniques used for human testing must be non-invasive and are therefore limited to certain experimental approaches (e.g., behavioral and neurophysiological). For use in environmental toxicology, the techniques must be sensitive to low level effects such as those encountered in the environment. Data derived from these measurements must also be interpretable, that is, they must provide some estimate or risk and not merely reflect exposure.

In the session dealing with the neurotoxicity of lead, key issues were discussed such as characterizing the neurobehavioral effects of lead exposure, defining dose-effect relationships, determining threshold levels for neurotoxicity, and addressing the reversibility of effects. Although there are still many unanswered questions, there is no doubt that considerable progress has been made in the last several years towards better defining the neurobehavioral consequences of lead exposure. Since environmental exposure to lead is such a great problem and since considerable research has been performed on the neurotoxicity of lead, these data should be exploited more systematically as a model for extrapolating from animals to man. The volumes of published data on this toxicant should help to direct us in our future studies. If one thing seems obvious, it is that we cannot afford to devote the research resources which have been expended on lead to the evaluation of all potential neurotoxicants.

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